MESCALINE

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MESCALINE is the principal alkaloid of peyotl (*Lophophora williamsii*), a cactus indigenous to Mexico and the southwestern areas of the United States. The dried tops of the cactus, often referred to as "mescal buttons," have long been used by natives of these areas as a panacea, and to promote trances and hallucinations. Sicé (1) has aptly stated that "man has often sought of drugs the marvels he could not find in the actuality of his monotonous life."

The first attempts to isolate the active principle of peyotl were reported by Lewin (2) in 1888. In 1896, Heffter (3) isolated three alkaloids, including mescaline, from the cactus. Spath (4), in 1919, succeeded in synthesizing mescaline (3,4,5-trimethoxyphenethylamine).

Mescaline is one of a number of naturally-occurring or synthetic compounds which, in humans, induces a "model pschosis." Studies of the psychosomimetic drugs are being pursued as one approach to the elucidation of the possible biochemical basis of mental disorders.

Biochemical Effects of Mescaline

Quastel and Wheatley (5) found that various amines including mescaline inhibited the oxidation of sodium lactate, pyruvate, and glutamate by minced guinea pig brain. These authors noted that mescaline had no effect on sodium succinate oxidation. Schueler (6) confirmed the observations of Quastel and Wheatley (5) and, largely on this basis, he used succinic acid in humans as an antidote in mescaline intoxication. Hallucinations were decreased in their complexity of design and intensity of color.

The effect of mescaline on respiratory enzymes of brain homogenates has been investigated. Clark *et al.* (7) reported that mescaline had no effect on succinic dehydrogenase or cytochrome C oxidase. Block *et al.* (8) stated that mescaline did not affect oxalosuccinic decarboxylase, oxaloacetic decarboxylase, or the transaminase

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which catalyzes the reaction from ketoglutarate and alanine to glutamate and pyruvate. Lewis and McIlwain (9) studied the effect of mescaline on the respiration of sliced guinea pig cortex. Electrical stimulation of the cortical slices greatly increased respiration and glycolysis; this increased activity was inhibited by 10^{-3} M mescaline.

Bain (10) reported that 10^{-3} M mescaline had no effect on either the uptake of oxygen or on the associated phosphorylation in preparations of mitochondria of the brains of rats respiring *in vitro* on a pyruvate substrate.

Bradley *et al.* (11) found that mescaline sulfate lowered the total nonprotein sulfhydryl concentration of rat liver but did not change brain levels significantly.

The biochemical effects thus far established for mescaline are nonspecific and offer little information concerning its characteristic mechanism of action.

In Vitro Metabolism of Mescaline

Rat, guinea pig, cat, and frog liver preparations have little or no capacity to oxidize mescaline, whereas rabbit liver will actively oxidize mescaline (12). The major product of this oxidative reaction, which occurs in the liver, is 3,4,5-trimethoxyphenylacetic acid (TMPA). The corresponding aldehyde apparently serves as a transient intermediate in this sequence (12). Blaschko (13) and Steensholt (14) doubt that monoamine oxidase participates in the oxidation of mescaline. Sourkes (15) has postulated that mescaline oxidase and diamine oxidase are identical. Zeller *et al.* (16) stated that mescaline may be inactivated *in vitro* or *in vivo* by either monoamine oxidase, diamine oxidase, or perhaps both. Bernheim and Bernheim (12) theorized that mescaline oxidase is not identical with aliphatic amine oxidase or mixed aromatic amine oxidase. The observations supporting this assumption may be summarized as follows: (a) tyramine oxidase catalyzes the oxidation of various amines but not mescaline; (b) addition of mescaline to a saturated amine oxidase substrate increases the rate of oxidation; (c) unlike amine oxidase, mescaline oxidase is not present in all tissues.

Daly *et al.* (17) have elucidated the *in vitro* demethylation of mescaline and the *in vitro* methylation of its demethylated congeners. Enzymatic O-methylation of 3,4,5-trihydroxyphenethylamine with rat catechol O-methyltransferase gives rise to 3,5-dihydroxy-4-methoxy-

phenethylamine, as well as small amounts of 3,4-dihydroxy-5-methoxyphenethylamine and 3,4-dimethoxy-5-hydroxyphenethylamine. Enzymatic O-methylation of 3,4-dihydroxy-5-methoxyphenethylamine forms 3,4,-dimethoxy-5-hydroxyphenethylamine. Enzymatic O-demethylation of mescaline, using a preparation of rabbit liver microsomes and supernatant, forms small amounts of 3,4-dimethoxy-5-hydroxyphenethylamine and 3,5-dimethoxy-4-hydroxyphenethylamine. A preparation of microsomes and supernatant will also oxidatively deaminate mescaline to TMPA.

Creveling *et al.* (18) have found that mescaline can be hydroxylated by dopamine-β-oxidase to yield mescalol.

Protein Binding

Investigations have furnished evidence that C^{14}-labeled mescaline is incorporated into mouse tissue protein *in vitro* (19). Brain will incorporate mescaline *in vitro* but not *in vivo*. The "blood-brain barrier" may constitute a limiting factor in the uptake of mescaline by the intact brain.

In an atmosphere of nitrogen, liver homogenates did not incorporate mescaline. However, when the homogenates were placed initially in an oxygen atmosphere and then transferred to a nitrogen atmosphere, mescaline was incorporated (19).

Heating liver tissue to 50°C. for 10 minutes increased incorporation two to ten-fold, depending on the pH. Heating to 100°C. before addition of mescaline prevented incorporation. This was interpreted as indicating that there is an inhibitor for the incorporation which may be partially or totally destroyed at 50°C., whereas, heating to 100°C. destroys the incorporating enzyme system. Tyramine and iron (II) plus citrate increases incorporation of mescaline, possibly due to binding of the inhibitor (19).

Isonicotinic acid hydrazide, an amine oxidase inhibitor, had no effect on the incorporation of mescaline, which indicates that amine oxidase is apparently not an inhibitor of mescaline incorporation (19).

Cathepsin, ATP, respiration, glycolysis, and ATP-generating systems had no effect on mescaline incorporation, indicating a different process from that responsible for amino acid incorporation. Microsomes, which are active in amino acid utilization, bind mescaline weakly; nuclei, which do not utilize amino acids, bind mescaline strongly (19).

Block (20) has postulated that mescaline is oxidized to an aldehyde, which forms a Schiff base with free amino groups of protein. The Schiff base either dissociates into an aldehyde, which would be further oxidized to an acid, and the protein, or dissociates to mescaline and the oxidized protein.

Fischer (21) found that mescaline has no affinity for wool protein as do certain other hallucinogenic agents.

If mescaline acts in a protein bound form, tolerance might be expected upon repeated administration. Acute tolerance to mescaline, administered hourly, was measured by arterial blood pressure reduction in dogs. The fall in blood pressure was 60 per cent of the initial response after the second administration of mescaline; subsequent responses decreased further to 47, 30, and 12 per cent of the initial response (22).

Speck (23) found that tolerance did not develop to the hypoglycemia and bradycardia produced by chronic administration of mescaline to rats.

In Vivo Metabolism

Block *et al.* (24) observed that relatively large amounts of mescaline appeared in the liver and kidneys immediately after intraperitoneal injection. Small quantities were found in brain, spinal cord substance, blood cells, and plasma. Different tissues attained maximal concentration of mescaline at various times after administration of the alkaloid. Block *et al.* (8) found that mice excreted 79.4 per cent of injected mescaline as the unaltered amine, 16.2 per cent as TMPA, and 4.4 per cent as an unidentified substance. There was no measurable $C^{14}O_2$ in the expired air of mice treated with C^{14}-labeled mescaline.

The mouse excretes mainly unchanged amine after the administration of mescaline, the rat mainly TMPA (8). Rat urine, collected over a 40 hour period after the intraperitoneal administration of radioactive mescaline, contained 72.4 per cent TMPA, 18.4 per cent mescaline, and 9.1 per cent of an unidentified substance. Goldstein *et al.* (25) and Friedhoff and Goldstein (26) found 3,4,5-trimethoxyphenylethanol in the urine of rats after the administration of mescaline. Friedhoff and Goldstein (26) demonstrated that either 3,4,5-trimethoxyphenylethanol, or 3,4,5-trimethoxyphenyl acetaldehyde produced potent biological effects, in rats and rabbits, at lower doses than required for mescaline.

The combined effect of mescaline and iproniazid could not be differentiated from that of an equal dose of mescaline alone. Thus an increase in the concentration of unmetabolized mescaline, due to inhibition of mescaline oxidase, indicates that the amine alone is not responsible for the characteristic effect. A combination of mescaline (10 mg./Kg.) and calcium carbimide (10 mg./Kg.) produced extreme reactions in rabbits, whereas mescaline alone (10 mg./Kg.) produced no observable effects. Inhibition of aldehyde dehydrogenase by calcium carbimide enhanced the pharmacologic effects of mescaline. Blockade of aldehyde dehydrogenase may increase the concentration of the aldehyde intermediate, and also may increase the concentration of trimethoxyphenylethanol. The effects observed could have resulted from either the alcohol or the aldehyde derivative of mescaline.

After oral administration of mescaline to dogs, Slotta and Muller (27) were able to isolate 38 per cent of the mescaline as TMPA but were unable to detect any of the parent compound in 24 hour urine. Cochin *et al.* (28) could not confirm this report; these workers found only trace quantities of TMPA and 24-46 per cent of the administered dose excreted as the parent compound. Spector (29) reported that oxidative deamination is the major pathway of metabolism (60 per cent) of mescaline in the dog, but that a significant amount of unchanged alkaloid is also excreted.

Cochin *et al.* (28) investigated the distribution of mescaline in the dog. After intravenous administration, there was a rapid decrease in the mescaline plasma level from a high initial concentration. This rapid fall was followed by a more gradual disappearance of mescaline from the blood, being complete in 6-8 hours. The amine was detected in the urine as soon as 30 minutes after intravenous administration, with the maximal rate of excretion occurring between 2 and 4 hours. The liver and kidneys contained the highest concentration of mescaline after 1 and 4 hours; the lowest levels were found in the brain and in the blood.

Slotta and Muller (27) identified and measured the excretion of TMPA in rabbits and dogs, but were unable to recover this compound from the urine of humans after ingestion of mescaline. Richter (30) found that man excreted 58 per cent of mescaline in the unchanged form. Small amounts of TMPA were also found. Harley-Mason *et al.* (31), using a paper chromatographic technique, failed to detect any TMPA in the urine of 6 human subjects given mescaline. They

reported finding small amounts of a glutamine conjugate of 3,4-dihydroxy-5-methoxyphenylacetic acid. Mokrasch and Stevenson (32) found, in blood and urine, an amine and an acid with three alkoxyl groups as the major metabolites of mescaline in man. Ratcliffe and Smith (33) have isolated 3-hydroxy-4,5-dimethoxyphenethylamine from human urine.

Mescaline may bind to protein in the human as it does in the mouse, and this binding may explain certain features of the mescaline recovery data. Solomon *et al.* (34) recovered an average of 30 per cent of mescaline in 6 human subjects within 8 hours. Richter (30), in one human subject, recovered 58 per cent of the administered drug after 24 hours. Harley-Mason *et al.* (31) recovered, from 6 human subjects, an average of 35 per cent of the amine within 24 hours.

Several cases of prolonged reaction (35) and delayed reactions (31) to mescaline have been reported. These may be due to the binding properties of mescaline or to liver damage (36).

Possible Mechanisms of Action

Block *et al.* (24), and Mokrasch and Stevenson (32), did not find a correlation between the levels of mescaline in the blood and urine of man and the central effects of the alkaloid. It has, therefore, been postulated that mescaline *per se* is not active but is converted to an active compound *in vivo,* or mescaline alters normal metabolism in such a manner as to cause hallucinations.

Quastel and Wheatley (5) suggested that malfunction of the liver, caused by mescaline, might lead to faulty detoxification of amines which in turn might have an untoward effect on brain respiration. This might lead to certain central nervous system disturbances.

Patzig and Block (37) postulated that mescaline combines with protein in the liver, the mescaline-protein complex being responsible for the characteristic central effects.

Speck (23) suggested that competition of mescaline for adrenergic receptors may be involved. Such a blockade may result in a disturbance of adrenergic mechanisms. Pellerin *et al.* (38) suggested that there may be a relationship between the methoxylated metabolites of the catecholamines and mescaline.

Mescaline and other hallucinogens decrease the rate of appearance of C^{14} in the brains of mice after intravenous or intraperitoneal administration of C^{14}-labeled glucose (39). This observation indicated that hallucinogens may decrease the transport of glucose

across the "blood-brain barrier" and produce changes because of the lowering of brain glucose.

Gordon (40) postulated that mescaline might be cyclized to an indole. Fisher (41) stated that mescaline is converted *in vivo* to an LSD-type compound which is responsible for the hallucinations. Biosynthesis of the LSD-type compound may be effected by the combination of partially demethylated mescaline with norepinephrine. It is not unlikely that a compound chemically related to mescaline, rather than a larger cyclized molecule, may be the active metabolite. Friedhoff and Van Winkle (42) have reported that 3,4-dimethoxyphenethylamine is found in the urine of some schizophrenics. However, there are no reports which indicate that this compound has hallucinogenic activity. Peretz *et al.* (43), and Shulgin *et al.* (44) reported that 3,4,5-trimethoxy-amphetamine will produce hallucinations in man.

Several analogs of mescaline have been reported which evidence no psychosomimetic activity. Reti and Castrillon (45) noted that N-dimethylmescaline will not produce hallucinations. Slotta and Muller (27) found that TMPA and 2,3,4-trimethoxyphenethylamine are not active *in vivo*.

Other possible metabolites of mescaline have been reported (17, 18, 26); however, their psychosomimetic potential has not been evaluated.

The mechanisms of the psychosomimetic activity of mescaline, and many other hallucinogenic compounds, remain a fertile field for future study.

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